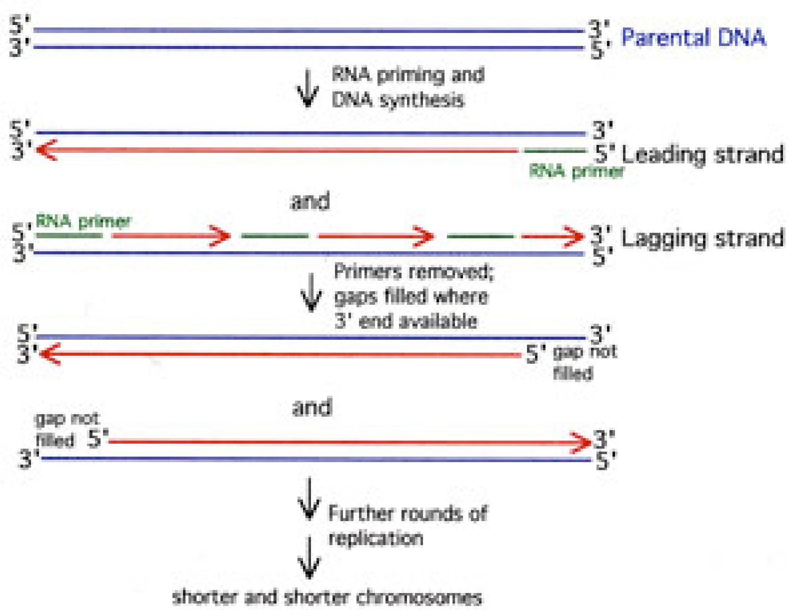
Telomeres and Telomerase

Every time a eucaryotic chromosome replicates, the new chromosomes thus formed lack a bit of DNA at each end. This occurs because DNA polymerase can only add nucleotides to the 3’ end. Recall from Unit 1 that both new strands are synthesized in the 5’ to 3’ direction, but the leading strand grows continuously while the lagging strand is produced in a short series of Okasaki fragments that are later joined by ligase. Replication must begin with an RNA primer at the 5’ end of the forming strand, so nucleotides can be added to the 3’ end of the primer. Later the RNA primers are removed. Those in the middle of the lagging strands can be filled after the primer is removed because there is DNA at the 5’ end to which nucleotides can join. But, there is no way to complete the 5’ ends of the daughter DNA strands, which means that each new chromosome has a gap at the 5’ end (see figure below). The ends of the chromosome have been clipped off. Repeated replications produce shorter and shorter chromosomes, and if a cell divides enough times, essential genetic material would be lost.



Prokaryotic chromosomes are circular, so there is always a DNA molecule to which a nucleotide can join and there is no problem. Eucaryotic cells, with their linear chromosomes, have solved the problem by having some **moderately repetitive DNA sequences** at the ends of their chromosomes.

Called **telomeres**, these are multiple repetitions of a short nucleotide sequence (TTAGGG in humans). The number of repetitions in a telomere varies between 100 and 2500. Every time a cell divides the telomere shortens. If human cells are put into cell culture, they will continue to grow and divide for a while. But each chromosome may lose between 50 and 200 base pairs of telomeric DNA with each round of replication and division. This shortening interferes with the stability of the chromosomes, and after about 20-30 divisions most cells are no longer able to divide properly. The same thing happens to cells within the body; certain cells will divide for a fixed-number-of-divisions, and then no longer. Telomeres may therefore be a limiting factor in the life span of certain tissues, and the organism as a whole.

Certain cells within the body, notably the germ line cells and cells of the bone marrow, do maintain their telomeres despite repeated cycles of replication and division. How are they able to do so? Such cells have a special enzyme, called **telomerase**, which catalyzes the addition of lost telomeric segments. It is an unusual enzyme; it has a molecule of RNA in its active site; this sequence acts as a template for the addition of new telomeric sequences (.e., it acts like an RNA primer). Interestingly enough, researchers have found telomerase in more than 90 percent of human cancers. Telomerase appears to stabilize telomere length in cancer cells, enabling the cells to divide immortally. Since most normal cells do not have this activity, telomerase is an attractive target for both cancer diagnosis and drugs designed to attack tumors specifically.

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